Assessment of platelet reactivity after the anthracycline-based chemotherapy via mean platelet volume: Does it act on anthracycline-induced cardiotoxicity?

Assessment of anthracycline-induced cardiotoxicity via MPV

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Abstract

Aim: Anthracycline-induced cardiotoxicity is the most frequent dose-limited toxicity. There has been numerous hypothesis about this matter. As an indicator of platelet size, mean platelet volume (MPV) is correlated with platelet reactivity, aggregation, and long-term atherosclerosis. We aimed to study whether the anthracycline triggers the elevation of MPV. Material and Method: Patients who had breast carcinoma and received anthracycline-based chemotherapy for only adjuvant setting were included. Age, disease stage, history of diabetes mellitus (DM), hypertension (HT) and body mass index (BMI) were recorded. Patients with systemic inflammatory rheumatic disorders, the symptoms of infectious diseases, cytopenia after the chemotherapyand, BMI over 40 and metastatic disease were excluded. Blood samples were collected for initial MPV value and after four cycles of adjuvant anthracycline treatment. Statistical significance of the associations was analyzed using Pearson correlation, Student's t, ANOVA tests and Wilcoxon signed-rank test. Results: Three hundred operated breast cancer patients were recruited in this study. Mean age was 49.1 (20-77). There was no significant correlation between age and initial MPV (r=-1.111, p= 0.056) or between BMI and initial MPV (r=0.023, p=0.697). Stage, DM, and HT did not affect initial MPV levels. Initial median MPV was 9.1 (6.2-12.8), and the last median MPV was 9.2 (6.1-12.9). According to Wilcoxon signed ranks test, positive ranks were found in 151 patients (p=0.003, Z=-3,002, based on positive ranks) after anthracycline therapy. Discussion: Anthracycline causes elevation in MPV value which is a marker of thrombocyte reactivation and atherosclerosis. This might be responsible for the possible long-term cardiotoxicity of anthracyclines.

Keywords

Platelet Reactivation; Doxorubicin; Cardiotoxicity; Mean Platelet Volume

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Introduction

The mechanisms of the antiproliferative and cytotoxic effects of the anthracycline antibiotics are DNA synthesis inhibition, free radical formation, DNA binding and alkylation, cross-linking, interference with DNA strand separation, direct membrane damage via lipid oxidation, and inhibition of topoisomerase II [1]. Anthracycline-induced cardiotoxicity is a dose-limited toxicity, and it presented classically with congestive heart failure vascular toxicity, and rarely as acute cardiotoxicities, such as electrocardiogram changes, arrhythmias, pericarditis and myocarditis syndromes [2]. Since there are no known effective protective agents and it leads to irreversible toxicity, it is managed based on preventive strategy according to cumulative dose. Also, it was known that increasing age is associated with increased risk of doxorubicin-related cardiotoxicity [3].

Although multiple mechanisms have been proposed for anthracycline-induced cardiotoxicity, it remains unclear which of these are effective in clinical context since most of the studies are on animals or in-vitro studies. Known mechanisms of the anthracyclines-induced cardiotoxicity are based on produced oxidative stress with membrane damage via lipid peroxidation, and inactivation of nitric oxide synthase. This ultimately leads to myocyte cell death even within hours after the anthracycline infusion according to human studies and cardiac remodeling develops with changing the extracellular matrix in the long-term [4-6]. Also, suppression of DNA, RNA, and protein synthesis triggers the cardiac sarcopenia, apoptosis, and necrosis in the heart tissue as in cancer cells [7]. On the other hand, decreased beta-adrenergic receptor stimulation after the anthracycline infusion contributes to decrease in the cardiac contractility [8]. Other explanations of cardiotoxicity have been proposed as some mediators such as platelet-activating factor, thromboxane A2 (TxA2), adenosine diphosphate (ADP), prostaglandins, histamine, and calcium according to in vivo and rat studies [9]. Mean platelet volume (MPV) is a significant marker showing a platelet activation. Larger platelet size is associated with more platelet function and activation which plays a crucial role in the pathophysiology of atherosclerotic disease and ultimately long-term cardiotoxicity. Thrombocyte activation and aggregation leads to proliferation and migration of smooth muscle cells from the media to endothelium in early stages of atherogenesis [10-12]. In this regard, we aimed to study whether the anthracycline-based chemotherapy triggers a higher MPV that indicates the platelet activity.

Material and Method

This retrospective study was designed to evaluate whether the anthracycline chemotherapy leads to platelet activation assessing through the measurement of MPV. A total of 300 operated breast cancer patients recruited in this study. All patients received anthracycline-based chemotherapy and were treated in the Gaziantep University Department of Medical Oncology between September 2011 and June 2016. The protocols were reviewed and approved by the Independent Ethics Committee of Gaziantep University Hospital.Patients were eligible for the study if they were over 18 years old, female, diagnosed with pathologically confirmed breast carcinoma, and received anthracycline-based chemotherapy for only in adjuvant setting. Other eligibility criteria were; an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, adequate hematologic and biochemical function, patients without hematologic disorders and without other malignancy, patients who did not receive any chemotherapy before.Patients with systemic inflammatory rheumatic disorders, the symptoms of infectious diseases (high C-reactive protein or white blood cell [WBC]), missing measured MPV before and after chemotherapy, cytopenia after the chemotherapy and body mass index (BMI) over 40, more than two times of upper limit of ALT and metastatic disease were excluded. Age, disease stage, history of diabetes mellitus (DM), hypertension (HT) and BMI were recorded. HT was defined as history of HT and/or systemic blood pressure measurements exceeding 140/90 mmHg. DM was defined as history or presence of diabetes and/or a fasting plasma glucose level higher than 7.0mmol/l (126 mg/dl) on two separate occasions, or a random glucose value of more than 11.1mmol/l (200 mg/dl) before administered anthracycline. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Obesity was defined as BMI of 30 or greater. Due to retrospective design, we could not reach the history of smoking and lipid profile.

In all patients, blood samples for complete blood count analyses were collected in 3.0 ml tubes containing ethylene dinitro tetraacetic acid (EDTA) and evaluated within 30 minutes before every administration of the anthracycline. Initial MPV values and initial WBC of all patients were recorded. Also, last platelet count and MPV values were noted after four cycles of adjuvant anthracycline treatment.All patients received intravenous (IV) 60 mg\m2 doxorubicin with 600 mg\m2 cyclophosphamide once every three weeks or IV 60 mg\m2 doxorubicin with 600 mg\m2 cyclophosphamide once every two weeks for four cycles.All statistical analyses were performed using SPSS version 16.0. MPV levels before first chemotherapy cycle and after the last chemotherapy cycle were recorded as continuous variables. Continuous variables were presented as mean±SD and compared using independent sample t-test between two groups. One-way ANOVA was used to compare three groups. Pearson correlation test was used to assess the relationship between two variables. Comparisons between parameters before and after anthracycline therapy were tested with the Wilcoxon signed-rank test. All P values were reported as two-tailed, with an accepted significance at less than 0.05.

Results

Three hundred operated breast cancer patients were recruited in this study. Mean age was 49.1 (20-77). There was no significant correlation between age and first MPV (r=-1.111, p=0.056). Respectively 9% (n=27), 42.7% (n=128) and 48.3% (n=145) of patients were stage I, II and III. There was no statistically significant difference between three groups according to first MPV levels. Stage I mean MPV was 9,46±1,27, stage 2 mean MPV was 9,23±1,23, and stage III mean MPV was 9,25±1,04 (p=0.568). There were 40 (13.3%) patients who have DM. First MPV of the patients with and without DM was 9,45±1,18 and 9,228±1,145 respectively (p=0.258). There were 20 (6.6%) patients who have HT. First MPV of patients with and without HT was 9,57±1,6 and 9,23±1,1 respectively (p=0.203). BMI

of 163 (54.3%) patients was under 30, and 137 (45.7%) were over 30. First MPV of patients with BMI under and over 30 was 9,22±1.17 and 9,29±1,13 respectively (p=0.633). There was no significant correlation between BMI and first MPV (r=0.023, p=0.697).

Initial median MPV was 9.1 (6.2-12.8), and last median MPV was 9.2 (6.1-12.9). According to Wilcoxon signed ranks test, positive ranks were found in 151 patients, and negative ranks were found in 149 patients P value was 0.003 (Z value:-3,002) based on positive ranks.

Discussions

The most common known vascular cardiotoxic agents are anti-metabolites (5-fluorouracil) and the anti-tumor antibiotics (bleomycin, doxorubicin). These agents affect not only tumor-associated endothelial cells but also endothelial cells of other tissues. This causes vascular toxicity such as pulmonary veno-occlusive disease, hepatic veno-occlusive disease, myocardial ischemia and infarction, cerebrovascular attacks, venous thromboembolic events [13]. Activation of coagulant factors, endothelial dysfunction, stimulation of fibroblasts and increase in levels of prothrombotic microparticles originating from endothelial cells or platelets could cause the direct vascular damage after the administration of anticancer drugs [14]. Biomarkers rise such as troponin-T, troponin-I, brain natriuretic peptide (BNP) and inactive amino-terminal pro-BNP (NT-pro-BNP) and phosphorylation of the histone H2A variant H2AX (termed γ-H2AX) is sensitive in detecting early asymptomatic cardiotoxicity in order to guide imaging assessment [15-17]. However, platelet activation has been not studied as a biomarker in the pathogenesis of chemotherapy-induced vascular toxicity and atherosclerosis in a humans study, until now. We, for the first time, evaluated the effect of doxorubicin on platelet reactivity through elevation of MPV after the chemotherapy in breast cancer patients. And we showed that anthracycline triggered an elevation in MPV.

Platelets play a crucial role in the pathogenesis of atherosclerosis and acute myocardial infarction (MI). Young platelets are characterized by an increased platelet volume, and more reactive platelet activity metabolically and enzymatically. They can lead to more platelet adhesion, aggregation, and acute vascular events. As an indicator of platelet size, MPV is correlated with platelet reactivity and aggregation [18]. Increased MPV is an independent risk factor for MI, stroke, and mortality from coronary artery disease and it has a poor prognosis after the MI and the coronary artery intervention especially patients with DM and HT [19-23]. Larger and more reactive platelets secrete a variety of mediators of inflammation, thrombosis, and coagulation such as neutrophil-activating peptide 2, interleukin-1, interleukin-6, P-selectin, intercellular adhesion molecule 2, Toll-like receptors, CD40, thromboxane A2 (TxA2), ADP and all of these mediators trigger platelet aggregation, inflammatory response, and tissue injury [9].

MPV, indicating a marker both inflammation and platelet reactivity, is also prognostic and predictive on recurrence in some cancer types via some mediators mentioned above. In malignant tumors, platelets can lead to tumor progression and angiogenesis. High MPV is associated with uncontrolled and metastatic disease [24-29]. Therefore, in this study, we excluded the un-operated and metastatic patients due to a probable rise in MPV value. In addition to patients with acute or chronic inflammatory disease and patient with a history of MI, and with an ejection fraction lower than 55% were excluded. After excluded conditions which might be the cause of platelet reactivity, we found increased MPV levels after completion of doxorubicin chemotherapy.

As previously shown in preclinic studies anthracyclines may cause a rise in the level of prostaglandins, thromboxanes, and leukotrienes through altering arachidonic acid metabolism [30]. And also preliminary data suggested that PAF may contribute to anthracycline toxicity. PAF is a strong activator for thrombocytes aggregation and a strong inducer of granules secreted from the thrombocytes [31]. Active thrombocytes release TxA2 and ADP, and this mediates the primary aggregation of the other pro-coagulation factors. Both granules are secreted from thrombocytes and appeared the TxA2 via released arachidonic acid from the cell membrane leading to irreversible thrombocyte aggregation. In this regard, the main question of this study is "Could MPV, which is an indicator of activated thrombocyte, be a predictive biomarker in anthracycline-induced platelet reactivity and long-term atherosclerosis". According to our study anthracycline treatment had a positively increasing effect on the level of MPV. Therefore, anthracycline may cause long-term atherosclerosis and cardiotoxicity through thrombocyte reactivation when evaluated with present preclinic studies. Also, metabolic syndrome parameters related to atherosclerosis were previously shown to get worse in the breast cancer patients receiving adjuvant anthracycline [32]. When our study is evaluated with previous studies, we have suggested that anthracyclines may cause long-term cardiotoxicity by provoking atherosclerosis.

The major limitations of this study are the retrospective design and hereby lack of assessment of other cardiac biomarkers together. At the same time, there is also a need for clinical and radiological demonstration of the development of atherosclerosis that may develop many years later. However, this study has importance to be the first clinical study showing increased MPV after the anthracycline chemotherapy. This study can pave the way for designing new prospective studies in this manner.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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